## REMARKS/ARGUMENTS

Claims 1-56 and 69-76 were pending. Claims 17-43, 45-50, and 51-56 are cancelled in this amendment without prejudice to future prosecution in this or another application. New claims 77- 88 are added.

The amendments to the claims add no new matter. The amendments to claim 1 are made to better characterize the invention. New sections (a) and (b) recite that the two polypeptide segments comprise at least 50 amino acids and are at least 95% identical in sequence. New section (c) corresponds to section (a) of the original claim, and has been amended to recite that the nucleotide sequences are at least 90% identical. Parts (b) and (c) of the original claim now appear in new claim 85. The phrase "wherein the polypeptide segment-encoding sequence of the synthetic gene is different from the polypeptide segment-encoding sequence of said naturally occurring gene" in original claim 1, has been deleted as redundant in view of the other amendments of the claim, but remains an accurate characterization of the claimed invention. Support for "at least 50" amino acids in claims 1 and 90 is found in the specification at at least paragraphs [0010], [0070], [00790] and [0276]. Support for the ranges in claims 82-85 is found in the specification at at least paragraph [0121]. Support for "at least 95% identical" and "at least 97%" identical in claims 78, 79 and 85-90 is found in the specification at at least paragraphs [0085] and [0279]. Support for "at least 100 residues" in claims 81, 86 and 88 is found in the specification at at least paragraph [0276]. Support for "less than 80%" or "less than 90%" sequence identity in claims 85, 86, 88, and 90 is found in the specification at at least paragraphs [0010] and [0277].

New claims 86-89 are product-by-process claims.

## OBJECTIONS TO THE SPECIFICATION

(a) Paragraphs [0364] and [0365] have been amended to denote "FLAG" as a trademark. Applicants note that in the specification FLAG was already in upper case as suggested by the Office, and was identified as an epitope tag.

(b) Paragraphs [0089], [0092], [0115] and [0310] have been amended as suggested by the Office.

(c) Paragraphs [0050], [0051], [0058] and [0068] have been amended as suggested by the Office.

## SEQUENCE COMPLIANCE

The Office Action mailed August 31, 2006 noted that sequences EPIAIV and YXFXXXRXW, and sequences disclosed in Figures 1B and 2 were not included in the original sequence listing filed April 16, 2004. Applicants note sequences EPIAIV and YXFXXXRXW were assigned sequence identifiers (SEQ ID NOS) 19 and 20, respectively, in the original sequence listing. However, sequences disclosed in Figures 1B and 2 were inadvertently omitted from the original sequence listing filed April 16, 2004.

In accordance with 37 C.F.R. §§ 1.821-1.825, Applicants submit a substitute sequence listing in CRF and paper formats incorporating sequences disclosed in Figures 1B and 2 that were inadvertently omitted from the original sequence listing submitted April 16, 2004.

The information contained in the substitute sequence listing in CRF format was prepared using the software program "FastSEQ for Windows" and the information therein is identical to that in the substitute sequence listing in paper format. As the sequence disclosure of the substitute sequence listing in either format does not go beyond that provided in the instant application this amendment adds no new matter.

REJECTIONS CITING 35 USC 112, FIRST PARAGRAPH

*Written Description*

Claims 1-15, 24, 39 and 69-76 were alleged not to be described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The inventors have disclosed a new method for making synthetic genes and has described novel synthetic genes made by this process. Using this method very large synthetic genes (e.g., > 20 kb) can be synthesized very rapidly, economically and accurately. A unique, identifying feature of the synthetic genes is that they can encode the amino acid sequence identical to that of a naturally occurring protein (e.g., myosin) but have a nucleotide sequence that differs dramatically from the naturally occurring gene (e.g., myosin gene). The synthetic methods disclosed by the instant inventors may be used to engineer very large synthetic genes with a variety of useful properties without undesirably changing the encoded protein.

Using this method, synthetic genes for essentially any naturally occuring polypeptide can be synthesized, having the unique features that distinguish it from genes found in nature. Indeed, the inventors described more than 85 kilobases of synthetic sequences. One of ordinary skill in the art reading the specification would immediately recognize this and understand that the inventors evidenced "possession" of the synthetic method and its products.

The Office has rejected claim 1 and other claims as allegedly not described in the specification. In articulating this rejection for written description the Office makes a number of arguments. The relevance of some of these arguments to the present invention is not clear. For example, the Office asserts that "the genus of claimed polypeptides encompasses widely variant species" and that "based on unlimited variations . . . one of skill would at best expect a protein that is different or at worst a protein that is not functional." As the instant claims are not directed to polypeptides this rejection is confusing. In this response Applicants endevor to address the concerns of the Office as completely as possible. Applicants reiterate their previously made

offer and request for a telephonic interview to explain aspects of the invention and to better address any concerns of the Office.

As Applicants understand it, the core of the concerns articulated by the Office are that claims that recite the term "polypeptide segment" (e.g., claim 1[1]) do not recite a *particular* polypeptide segment. The Office states that the claims encompass a large variable genus and asserts the skilled artisan cannot envision the detailed chemical structure of the genus encompassed. The Office also states "the specification fails to provide any additional representative species of the claimed genus to show that the application was in possession of the claimed genus." As noted above, the specification provides >85 kilobases of synthetic genes falling within the scope of the claims. It would be clear to one of skill in the art, with undergraduate knowledge of the genetic code and the relationship between DNA and amino acid sequences, and guided by the teachings of the specification providing detailed description of the design of synthetic genes that the inventors had possession of the invention claimed. The Office is respectfully asked to explain what purpose would be served by provision of an additional 85, or 100, or 1000 kilobases of synthetic genes.

As noted, the present inventors have disclosed a new method for making synthetic genes encoding naturally occuring protein sequences, and synthetic genes made by this method. The synthetic genes have identifying structural features which are recited in the claims such as, *inter alia*, a low level of sequence identity with naturally occurring counterparts.

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1 Claim 1, as amended: A synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring gene, and

a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are the same length and comprise at least 50 amino acids;

b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and

c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene is are less than 90% identical in nucleotide sequence.

The present specification teaches that the sequences of naturally occurring genes are known (for example, referencing GenBank, *see* paragraphs [0178] and [0352]). For illustration the specification provides numerous accession numbers from which one of skill can readily find protein sequences and corresponding gene sequences. Moreover, the specification provides a detailed description of several synthetic genes made according to the invention (see, e.g., Examples 7 and 9 and Tables 14A-B and 17A). These synthetic genes encoding nine large polypeptides (ranging from about 1,410 amino acids to >7,000 amino acids in length) with > 99.7 % sequence identity with the corresponding naturally occurring polypeptide but only 74-76% sequence identity with the naturally occurring gene.

The Office states "the specification fails to provide any additional representative species of the claimed genus to show that the application was in possession of the claimed genus." The Office appears to believe the written description requirement requires that the specification provide examples of an unspecified ("representative") additional number of naturally occuring polypeptides or genes. This is not a requirement of Section 112. In their decision in *Falkner v. Inglis* the Court of Appeals for the Federal Circuit stated:

> "a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention."[2]

The *Falkner* Court continued

> "Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences . . . satisfaction of the written

[2] Falkner v. Inglis (Fed Cir 2006) 79 USPQ2d 1001; 448 F3d 1357

description requirement does not require either the recitation or incorporation by reference."[3]

In *Falkner* an interference count was directed to vaccines comprising a poxvirus vector having a deleted or inactivated essential gene. Appellants argued that the Patentees had not described and enabled vaccines comprising a poxvirus vector having a deleted or inactivated essential gene because the patent did not identify *any* essential poxvirus genes or the inactivation of any such genes. In response, the Court held neither examples nor actual reduction to practice nor recitation of known structures nor incorporation by reference of literature describing known structures was required to comply with Section 112.

In another case, *Capon v. Eshhar*,[4] the Federal Circuit faced a similar issue and similarly ruled that written description does not require recitation of known sequences. In *Capon* claims were directed to chimeric DNA encoding single-chain chimeric proteins for expression on the surface of cells of the immune system. The chimeric DNA combined a first segment encoding all or a portion of a protein "expressed on the surface of cells of the immune system" (e.g., a lymphocyte signaling protein) and a second segment encoding the single-chain variable ("scFv") domain of "a specific antibody" (e.g., unspecified antibodies against "tumor cells," "virus infected cells," and the like).[5] The Board of Patent Appeals and Interferences held that neither party described "by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences which encode many protein domains" and that neither application in interference was in compliance with the written description requirement.

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[3] Falkner v. Inglis (Fed Cir 2006) 79 USPQ2d 1001; 448 F3d 1357

[4] Capon v. Eshhar 76 USPQ2d 1078 (Fed. Cir. 2005).

[5] Claim 1 of application No. 08/084,994 to Eshhar et al. is described. The claim reads:

1. A chimeric gene comprising a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells, which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFV domain binds to its antigen.

The *Capon* Court vacated the decision of the Board and held:

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.[6]

As in *Capon*, the present invention is not the discovery of naturally occurring genes, and recitation of specific gene sequences in the claims is neither necessary nor appropriate. Accessible literature sources, including Genbank, clearly provided, as of the relevant date, genes and their nucleotide sequences. Moreover, several exemplary large genes were described in detail. Applicants respectfully submit that any individual skilled in the art would recognize that Applicants had possession of the claimed invention.

*Enablement*

The rejection articulated by the Office in rejecting the claims as allegedly not enabled mirrors the rejection for alleged lack of description. The Office asserts that the "amount of experimentation required to practice the claimed invention is undue as the claims encompass a large variable genus of polypeptide segments and nucleic acid segments encoding said polypeptide" and that a "large quantity of experimentation [would be] necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity .

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[6] Capon v. Eshhar

. ." First, Applicants respectfully submit that clearly it is impossible to make an "infinite" number of species, with or without experimentation, and that enablement does not require that every species encompassed in a claim be made.[7] What is more relevant is that the Office has not provided a single example of a synthetic gene of the invention that would require undue experimentation to make. On the contrary, the specification provides a detailed description of how to make and use the claimed synthetic genes. The enabling disclosure provides working examples of *more than 85 kb* of synthetic genes. Applicants respectfully submit that one of ordinary skill in the art (who would of course have knowledge of the genetic code and the basic principles of molecular biology) would find that the specification is enabling.

The Office also discusses at considerable length whether potential changes in a protein's amino acid sequence could be "tolerated" (by which the Office means, would not be deleterious to the activity of a protein). As an initial matter, the claims are not directed to a protein, let alone a protein with a specified activity, nor is the claim directed to the discovery of a new protein structure.[8] It should be clear that the invention is directed to *synthetic genes* that encode a polypeptide segment that has substantial (e.g., 95% - 100%) identity to a naturally occurring protein segment. Even if, *arguendo*, an occational polypeptide does not retain the biological activity of the naturally occurring counterpart, this is irrelevant to the question of whether the teachings of the specification enable one of skill to make and use the claimed synthetic gene. Moreover, the person of skill has complete control over the polypeptide sequences encoded in the synthetic gene. Any "change" in a protein's amino acid sequence would be a change predicted, desired and intended by the person of skill practicing the invention.

## REJECTIONS CITING 35 USC 112, SECOND PARAGRAPH

Claims 1, 7, 14, 24, 39 and 75 were rejected under 35 U.S.C. 112, second paragraph.

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[7] Applicants also note that virtually any claim with "comprising" language could be said to encompass an infinite number of species.

[8] The Office appears to have confused the gene sequence and the polypeptide sequence (see Office Action, page 9, line 12 - page 12, line 7).

Applicants respectfully traverse the rejection of claims 1, 7 and 75. The Office states that it is unclear what reference polypeptide is being referred to because no structure is recited in the claims. Applicants believe the claim is clear. In claim 1, it is explicit that the "reference polypeptide" is a naturally occurring polypeptide. The term "reference" is simply a term of art used to distinguish the reference polypeptide from the polypeptide encoded by the synthetic gene; the claim could as easily use the terms "first polypeptide" and "second polypeptide." Although the claim 1 does not recite a specific amino acid sequence, this does not render the claim unclear. Moreover, Applicants disagree that no structural features are recited. Clearly, a "polypeptide" connotes a particular structure. In addition claim 1 has been amended to recite that the reference polypeptide seqment is at least 50 amino acids in length (claim 1),

Claim 14 has been amended to provide antecendent basis for the abbreviation "PKS" thereby overcoming the rejection.

The rejection of claims 24 and 39 is moot in view of the cancellation of these claims in response to a restriction requirement imposed by the Office.

## ART REJECTIONS

Claims 1-4, 7 and 75 stand rejected under 35 USC 102(b) as allegedly anticipated by one or more of Wingfield et al., Mandecki et al., or PCT Publication WO/9313663 (Abbott). Applicants traverse.

The rejected claims were directed to a synthetic gene that, *inter alia*, has a "polypeptide segment-encoding sequence . . . less than **about** 90% identical to [a corresponding] polypeptide segment-encoding sequence of [a] naturally occurring gene . . ." In rejecting the claims the Office asserts "the specification does not define the range of 'about.' The Office additionally states:

**"The art recognizes the term 'about' to be extendible to a range of ± 10"**

The Office then asserts that:

> ..."**about 90%" can mean 100% or can mean 80%.**"

The Office provides no authority for these surprising assertions, nor suggests what "art" allegedly recognizes this. Applicants emphatically submit that the Office interpretation is not even remotely plausible. The Office is requested to produce documentary evidence to support this assertion and/or provide an affidavit under 37 CFR 1.104(d)(2) explaining the basis for the assertion.

Paragraphs 12, 13 and 14 of the Office Action, offer the following basis for rejection:

> **"Therefore, less than about 90% can be any percent approaching 80%, which, means 99%, or 98% meets this limitation."**

Applicants respectfully neither understand this statement nor understand how this statement supports the instant rejections.

Applicants respectfully submit that the Office position is a unsupported and unsupportable. Moreover, even if, *arguendo*, this astounding assertion were accepted, the Office has still failed to articulate any *prima facie* basis for anticipation. That is, even accepting the Office position that less than about 90% actually means 100%, the Office has failed to even suggest that the cited references disclose a synthetic gene meeting the requirements of parts (b) and (c) of claim 1 as it was pending. Applicants respectfully request that the Office revisit this rejection.

Finally, of the three references cited in the §102 rejection, two were previously cited by the present Examiner during her examination of the the same claim set in PCT/US03/30940 (the PCT counterpart of the instant application). Applicants provided a detailed discussion in the PCT phase. In Applicants' response to the Restriction Requirement[9] of the instant application these references were again discussed as a courtesy and to expidite and facilitate examination.

[9] Filed March 20, 2006.

However, Applicants' discussion in the response to restriction requirment of why the Wingfield and Abbott references are unlike the present invention appears to have been utterly ignored by the Office. Applicants respectfully request that the Office reconsider the current rejections and revisit the response to restriction requirement.

To briefly summarize, the Winfield et al. reference described a polypeptide segment corresponding to residues 27-154 of gp41 of SIVmac 239. The Winfield polypeptide segment corresponds to the 127-residue polypeptide segment of the naturally occurring gene and differs from same at two residues. The 366 nucleotide DNA sequence encoding residues 27-149 in the naturally occurring gene differs from a DNA sequence mutated at C86A, C92A by 4-6 bases.[10] Thus the mutated sequence is 98.4-98.9% identical to the naturally occurring gene. This reference did not anticipate the claims, which recite polypeptide segment-encoding sequences of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence.

WO 93/13663 ("Abbott") described a method of directing biosynthesis of specific polyketides. The method involves isolating a polyketide biosynthetic gene (i.e., a gene that encodes a protein involved in polyketide biosynthesis) from a microorganism. See abstract. The gene may be modified using conventional molecular biology methodology. See pages 9-12 of the WO 93/13663 publication. Nothing in WO 93/13663 suggested a *synthetic gene* having the properties of the polynucleotide of instant claim 1. Rather, any given polypeptide segment-encoding sequence in the recombinant gene of WO 93/13663 has nearly exact correspondence polypeptide segment-encoding sequence of the naturally occurring gene from which it is directly derived. WO 93/13663 is not relevant to the present invention. Applicants further note the Office has not explained how claim 7 is allegedly anticipated by Abbott.

Mandecki described a method for synthesis of a gene using a technique of oligodeoxynucleotide (oligo)-directed double-strand (ds) break repair which as used in synthesis of a gene fragment encoding the N-terminal 143 amino acid residues of HIV p41. The Office asserts Mandecki anticipates the claimed invention because "The art recognizes the term 'about'

to be extendible to a range of ±10 thus, about 90% can be interpreted as "80, 81, 82, 83, 854, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%". Therefore, less than about 90% can be any percent approaching 80%. Based on the range encompassed in the claims the cited reference teaching mutations would achieve a percentage in this range." Applicants have explained that the Office's assertions concerning the meaning of "about" incorrect and unsupported. Should the Office believe the rejection based on Mandecki is not completely addressed by this, the Office is requested to clarify the basis for rejection.

Applicants note that to expedite prosecution claim 1 has been amended and does not recite "about." However, the term "about" remains in amended claim 75 and new claim 88. Applicants submit that one of skill in the art would understand "about" 80% to mean 80% ± 1%.

## RESTRICTION REQUIREMENT

Applicants reiterate their traverse of the restriction requirement. In addressing Aplpicants' previously submitted remarks, the Office states, *inter alia*, that "arguments presented using the PCT is not germane to Restriction Practice." The Office is respectfully reminded that the "restriction requirement" mailed 20 December 2005 justified restriction by citing the PCT rules (e.g., "The inventions . . . do not relate to a single general inventive concept under PCT Rule 13.1 . . . ."). Applicants responded to the assertions made by the Office, specifically by explaining that the Wingfield reference did not anticipate the claims. (As noted above, the Office appears not to have considered Applicants' comments.) The Office is requested to now clarify the basis asserted for restriction. Applicants reserve their right to petition for rejoinder.

## INTERVIEW

Applicants request the courtesy of an interview to discuss the merits of this case. Applicants' representative will contact the Examiner to arrange for a mutually convenient time.

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[10] The precise nature of the codon change is not clear from the reference.

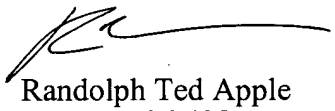
## CONCLUSION

For the reasons provided above, Applicants respectfully request that the claims now pending be examined and a Notice of Allowance issued.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Date: February 27, 2007

Respectfully submitted,



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